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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,844	02/08/2002	Lawrence M. Kauvar	388512010500	1387

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,844	KAUVAR, LAWRENCE M.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-11 in the reply filed on August 20, 2004 is acknowledged. The traversal is on the ground(s) that Applicant finds it difficult to see how examination of Groups I and II together would place any kind of undue burden, or any burden al all, on the Office. This is not found persuasive because of reasons of record and further because while the searches would be expected to overlap, there is no reason to expect the searches to be coextensive. Further, the search for the different methods requires different search terms and a different search strategy that creates a burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 10 "the affinity" there is insufficient antecedent basis for this limitation.

Claim 1 is vague and indefinite because it is unclear if the demitopes are the same or different demitopes. For example, if both demitopes are the same (*i.e.* one

demitope is a variable light chain and the second demitope is a variable light chain) does a paratope still form . It appears that the demitopes would have to be complementary in order to form a paratope (i.e. one variable light chain and one variable heavy chain). Please clarify.

Claim 5 is vague and indefinite because of the use an acronym: ie NMR. Although the term may have art-recognized meanings, it is unclear if applicant intends to claim the prior art definitions. The term should be defined in its first instance.

Claim 6 is vague and indefinite because it is unclear how a toxin provides an immediate detectable signal. The specification on page 9 discloses that when assembly has occurred, the concentration of toxin is reduced. The inactivation of the toxin then permits cell growth so that only cells in the presence of positive interactions will proliferate. The growth of cells requires time and therefore, it is unclear how the detectable signal is immediate. Please clarify.

Claim 9, the recitation "small molecule" is vague and indefinite. It is unclear what is considered to be a small molecule.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-4 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arndt et al., (Helix-stabilized Fv (hsFv) Antibody Fragments, J. Mol. Biol. (2001) 312, 221-228) in view of Kranz et al Proc. Natl. Acad. Sci. USA, vol. 78, No. 9, pp. 5807-5811 1981).

Arndt et al disclose a WinZip-B1 (first substance) coupled to a VL domain (first demitope) and a WinZip-A2 polypeptide (second substance) coupled to a VH domain (second demitope). Arndt et al disclose that the interaction of the WinZip-B1 polypeptide and WinZip A2 interact to form a coiled-coil which brings the VL (variable light chain) and VH (variable heavy chains) domains into orientation to form a functional protein containing an antigen binding site (paratope). Arndt et al disclose determining the functionality of the protein (p. 224).

Arndt et al differ from the instant invention in failing to teach the presence of a reporter and wherein said reporter generates an immediate detectable signal when bound to the paratope.

Kranz et al disclose that the associate of heavy and light chains form a functional antigen-binding site. Kranz et al disclose combining the light and heavy chains with

fluorescein (reporter). Kranz et al disclose that the formation of the light and heavy chains provides for binding to the fluorescein which is significantly quenched when bound (p. 5808).

It would have been obvious to one of ordinary skill in the art to incorporate a reporter as taught by Kranz et al into the method of Arndt et al because Kranz et al shows that the addition of reporter provides monitoring the formation of an active site and one of ordinary skill in the art would recognize that providing the reporter as taught by Kranz et al would provide for a reduction in the amount of steps required for determining the formation of an active binding site and one of ordinary skill in the art would have a reasonable expectation of success incorporating a reporter as taught by Kranz et al into the method of Arndt et al.

With respect to the first substance is a small molecule and the second substance is a protein as recited in the instant claims. Since it is unclear what applicant intends by small molecule and since Arndt et al teaches interacting polypeptides (protein), the above references read on the instantly recited claims.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arndt et al and Kranz et al in view of Koide (US 6,673,901).

See above for teachings of Arndt et al and Kranz et al.

Arndt et al and Kranz et al differ from the instant invention in failing to teach the detectable signal is an alteration of NMR spectrum.

Koide teaches nuclear magnetic resonance (NMR) experiments to identify the contact between an antibody and a target molecule such as fluorescein (col 28). Koide

teaches that this provides for information that can be used to improve the affinity and specificity of the antibody.

It would have been obvious to one of ordinary skill in the art to incorporate NMR into the modified method of Arndt et al because Koide teaches that NMR experiments are used to identify the contact between an antibody and a target molecule such as fluorescein and Koide shows that this provides for information that can be used to improve the affinity and specificity of the antibody. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating NMR as taught by Koide into the modified method of Arndt et al for detecting alterations in the signal.

7. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arndt et al and Kranz et al in view of Griffin et al (Specific Covalent Labeling of Recombinant Protein Molecules inside Live Cells, Science Vol 281 10 July 1998).

See above for teachings of Arndt et al and Kranz et al.

Arndt et al and Kranz et al differ from the instant invention in failing to teach the method is conducted intracellualary.

Griffin et al teaches a method of labeling a ligand inside a cell by introducing a fluorescein molecule which binds to the protein. Griffin et al teaches detecting the signal of the label after binding to the protein. Griffin et al teaches that this provides a system for modifying a protein so that it can be singled out from many other proteins inside live cells (p. 269).

It would have been obvious to one of ordinary skill in the art to incorporate labels as taught by Griffin et al into the modified method of Arndt et al because Griffin et al

shows that this provides for modifying a protein so that it can be singled out from many other proteins inside live cells.

8. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arndt et al and Kranz et al in view of Empedocles et al.

See above for teachings of Arndt et al and Kranz et al.

Arndt et al and Kranz et al differ from the instant invention in failing to teach the immediate detectable signal is observed by wide-field microscopy.

Empedocies et al teaches that wide-field microscopy provides that the signal can be integrated for relatively long periods of time and that wide-field microscopy is particularly beneficial when detecting semiconductor nanocrystals, since they do not photobleach. Empedocies also teaches the use of semiconductor nanocrystal conjugates in binding assays and shows that these semiconductor nanocrystals are superior to fluorescein (Fig. 3).

It would have been obvious to one of ordinary skill in the art to incorporate semiconductor nanocrystal conjugates and wide-field microscopy as taught by Empedocies et al into the method of Arndt et al and Kranz et al because Empedocies et al shows that semiconductor nanocrystal conjugates are superior to fluorescein and that wide-field microscopy provides that the signal can be integrated for relatively long periods of time and that wide-field microscopy is particularly beneficial when detecting semiconductor nanocrystals, since they doe not photobleach.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Cohen et al (US 2004/0086503) disclose the VH domain of an anti-IGF-IR antibody linked to a first polypeptide, while the VL domain of an anti-IGF-IR antibody linked to a second polypeptide that associates with the first polypeptide in a manner in which the VH and VL domains can interact with one another to form an antibody binding site (p. 19, paragraph 0191).

Leung (US 2002/0076406) teaches bringing together a variable light chain region and a variable heavy chain region to form a functional target binding site.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
November 10, 2004

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11/12/04